Remarks/Arguments

Claims 44-46 and 49-51 are pending in this application and are rejected on various grounds. No new matter has been added due to amendments to the specification. The rejections to the presently pending claims are respectfully traversed.

Priority determination

Applicants submit the appropriate pages from PCT/US/00/03565, filed 2/11/00 for the Examiner to verify the priority claim. Accordingly, this application is entitled to an effective filing date of at least **February 11, 2000**.

Claim Rejections – 35 U.S.C. § 101 and 112, first paragraph

Claims 44-46 and 49-51 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 44-46 remain rejected under 35 U.S.C. §112, first paragraph allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be

careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

As discussed previously, Applicants rely on the gene amplification data for patentable utility for the PRO304 protein. The gene amplification results are set forth in Table 9.

The Examiner has asserted that "Applicants have not provided any declaratory evidence of the 2.00-3.204 fold amplification, most especially how the delta Ct values at page 230-234 have

been extrapolated to three decimal places of amplification and (b) have failed to provide fact or evidence that the figures are "way above figures considered significant", nor what such figures are deemed to signify. For the reasons outlined below, Applicants respectfully disagree.

Applicants hereby submit an executed Declaration by Dr. Audrey Goddard, and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> "It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy" (Emphasis added).

Thus, the Goddard declaration states the critical level of amplification of a tumor marker should be at least 2-fold. Further, the present specification states in the passages bridging pages 222 and 223 that:

> "The results of TaqMan PCR are reported in Ct units. **One unit corresponds to** one PCR cycle or approximately **2-fold amplification**, relative to control, 2 units correspond to 4-fold amplification, 3 units to 8-fold, etc. amplification."

Thus, the fold amplification for the Ct units can be calculated as follows based on the above information: For PRO304, 1.00- 1.68 Ct units corresponds to $2^{1.00}$-$2^{1.68}$ - fold amplification or **2.00 fold to 3.204-fold** amplification in 7 primary lung tumors, figures which are way above figures considered significant according to the Goddard declaration. Hence, these data clearly support a role for PRO304 nucleic acids as a lung tumor marker.

The Examiner further quotes an article by Sen to demonstrate that "a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely by an

indication that the cancer tissue is aneuploid." Again, Applicants respectfully disagree.

Applicants submit that, as noted by the Examiner and the Sen article, aneuploid tissues are cancerous or pre-cancerous. The present invention is directed to proteins useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Even if aneuploid tissues were to predict a propensity for cancer, the instant proteins and their antibodies are still useful as diagnostic tools. Applicants refer to the attached declaration by Avi Ashkenazi, Ph.D., a co-inventor of this application, who says that:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes."

A *prima facie* case of lack of utility has not been established

The Examiner further holds the position that "an increase in nucleic acid copy number is not predictive of a similar association for protein... The art does not recognize that protein levels are increased when gene amplification occurs." The Examiner relies on exemplary literature reports like Pennica, Konopka and Haynes *et al.* for support and hence concludes that the PRO304 polypeptides lack utility. Applicants traverse.

According to the Examiner, Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, ... In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for

a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

The Examiner also cites the Konopka *et al.* abstract to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general but to single genes or genes within a family and thus, their teachings have been misrepresented in this rejection.

Finally, the Examiner states that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." Applicants respectfully further point out that, Haynes found that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there was a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation was "not linear" and hence, Haynes states that "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data showed that a positive correlation exists between mRNA and protein levels (although the correlation is not linear and hence, cannot be used to predict protein levels). Further, the Haynes data meets the "more likely than not standard" since it studies 80 proteins and shows "a general positive trend" in most proteins. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, is typical, based on Pennica, Konopka and Haynes. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Haynes *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, just as in Haynes, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Ornfoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornfoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO304 gene, that the PRO304 protein is

concomitantly overexpressed. Thus, Applicants submit that the PRO304 proteins and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the antibodies for diagnosis of cancer.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or

over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO304 polypeptide and antibodies that bind to it, for example, in detecting over-expression or absence of expression of PRO304. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies of the instant invention based on the instant disclosure.

Thus, Applicants have demonstrated gene amplification data that clearly support a role for PRO304 nucleic acid and polypeptides as lung tumor markers. Accordingly, the present 35 U.S.C. §101/ 112, first paragraph utility rejections should be withdrawn.

Deposit requirement

Claims 44-46 and 49-51 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one skilled in the art how to make or use the invention.

Applicants submit that the present amendments to the specification, as per the Examiner's suggestions, should obviate this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C35). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 16, 2004

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